Luspatercept (myelodysplastic syndrome)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Luspatercept (myelodysplastische Syndrome) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback of persons concerned or patient organizations was received within the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
ESA	erythropoiesis-stimulating agents
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
Hb	haemoglobin
HI-E	haematologic improvement–erythroid
IPSS-R	reviewed international prognostic score system
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MDS	myelodysplastic syndromes
pRBC	packed red blood cells
PRO	patient-reported outcome
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
WHO	World Health Organization

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug luspatercept. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 15 May 2023.

Research question

The aim of the present report is to assess the added benefit of luspatercept versus the appropriate comparator therapy (ACT) in adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts who had unsatisfactory response to or for whom erythropoetin-based therapy is ineligible.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of luspatercept

Therapeutic indication	**ACT**[a]
Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS with ring sideroblasts, who had unsatisfactory response to or for whom erythropoetin-based therapy is ineligible	Transfusion therapy with packed red blood cells (pRBC) as needed in combination with chelation therapy in accordance with the approval
a. Presented is the ACT specified by the G-BA. b. It is assumed that the patients are in need of treatment and that an allogeneic stem cell transplantation is not an option for them at the time of treatment with luspatercept. If necessary, the use of epoetin, possibly in combination with G-CSF, may also be indicated in the present therapeutic indication. G-BA: Federal Joint Committee; G-CSF: granulocyte colony-stimulating factor; MDS: myelodysplastic syndrome	

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for deriving added benefit.

Study pool and study design

The MEDALIST study is used for the benefit assessment. The MEDALIST study is a double-blind RCT comparing luspatercept with placebo in adults with very low, low and intermediate-risk MDS with ring sideroblasts in accordance with the reviewed international prognostic score system (IPSS-R) for MDS. Moreover, patients had to have transfusion-dependent anaemia due to MDS. The included patients had either received prior treatment with erythropoiesis-

stimulating agents (ESA) (as mono/combination therapy) and had not shown adequate response, were not suitable for ESA or had to be intolerant to ESA treatment.

Overall, 229 patients were included in the MEDALIST study and randomly allocated in a 2:1 ratio to treatment with luspatercept (N = 153) or placebo (N = 76). Treatment with luspatercept was largely in compliance with the specifications of the Summary of Product Characteristics (SPC). Deviating from this, a dose reduction below 0.8 mg/kg was permitted, but this only occurred in 1 patient. Moreover, treatment with luspatercept in accordance with the SPC should be discontinued in those patients who do not notice a reduction in the transfusion burden after 9 weeks of treatment (3 doses) with the highest dose (1.75 mg/kg). Since the assessment of the clinical benefit in the MEDALIST study took place in Week 25, it is possible that patients in the luspatercept arm received 2 luspatercept doses with the initial dose of 1.0 mg/kg (6 weeks), 2 consecutive doses of 1.33 mg/kg (6 weeks) and, in deviation, 4 instead of 3 consecutive doses of 1.75 mg/kg (12 weeks) up to and including Week 24 in accordance with the SPC.

In both study arms, platelet transfusions were allowed at the investigator's discretion in the case of low haemoglobin (Hb) levels, anaemia-related symptoms or comorbidities. In combination with the administration of packed red blood cells (pRBC), chelation therapy could be used at the discretion of the investigator in accordance with the approval.

After randomization, the MEDALIST study is divided into a treatment phase (comprising a primary treatment phase and an extension phase) and a (long-term) follow-up phase. The planned duration of the primary treatment phase was 24 weeks. From week 25, treatment was continued in the extension phase if there was a proven clinical benefit (e.g. reduction in packed red blood cell transfusion burden/increase in Hb level from baseline) and absence of disease progression (assessed at Week 25 and at every 8th cycle, Day 1 of the extension phase). Patients with treatment discontinuation in the primary treatment phase or in the extension phase were included in the (long-term) follow-up phase, which was planned to last until 3 years after the last dose of the study medication. A switch from placebo to luspatercept was not allowed at any time point in the study.

Primary outcome of the MEDALIST study was transfusion avoidance of ≥ 8 weeks during the primary treatment phase. Additionally, patient-relevant outcomes were recorded on mortality, morbidity, health-related quality of life and side effects.

The company presented analyses on the 26 November 2020 data cut-off. Since 100 (65%) patients in the luspatercept arm but only 26 (34%) in the placebo arm continued to be treated with the study medication after the visit at Week 25, analyses up to and including Week 24 or Week 25 were used for the present benefit assessment for all outcomes whose observation period was linked to the end of treatment (concerns the outcome categories of morbidity,

health-related quality of life and side effects). For the outcome category of mortality, overall survival on the basis of a time-to-event analysis for the final data cut-off (26 November 2020) was used.

Risk of bias and certainty of conclusions

The risk of bias across outcomes for the MEDALIST study is rated as low. The outcome-specific risk of bias of the results is rated as low except for the outcomes on symptoms and health-related quality of life (each recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 [EORTC QLQ-C30]).

Results

MortalityOverall survival

For the outcome of overall survival, there was no statistically significant difference between the treatment groups up to the final data cut-off (26 November 2020). There was no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Transfusion avoidance

Up to and including Week 24, a statistically significant difference was found in favour of luspatercept in comparison with the ACT for the outcome of transfusion avoidance. There is an indication of added benefit of luspatercept in comparison with watchful waiting.

Symptoms (EORTC QLQ-C30)

For the symptoms outcomes, recorded with the EORTC QLQ-C30, responder analyses were used on both improvement and worsening by ≥ 10 points at Week 25.

Fatigue and insomnia

For the outcomes of fatigue and insomnia, there was no statistically significant difference between treatment groups for the analyses on the improvement from baseline. For the analysis of worsening compared to the start of the study, a statistically significant difference to the disadvantage of luspatercept compared to the ACT was shown for the outcome “fatigue”, whereas a statistically significant difference in favour of luspatercept over the ACT was shown for the outcome “insomnia”. However, for these two outcomes, this difference is no more than marginal. In each case, there was no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Nausea and vomiting, pain, dyspnoea, appetite loss, constipation and diarrhoea

For the analyses on both improvement and worsening, no statistically significant difference between the treatment groups was shown for each of the following outcomes: “nausea and

vomiting", "pain", "dyspnoea", "appetite loss", "constipation" and "diarrhoea". In each case, there was no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

For the outcomes on health-related quality of life, recorded with the EORTC QLQ-C30, responder analyses were used on both improvement and worsening by ≥ 10 points at Week 25.

Physical functioning

For the outcome of physical functioning, no statistically significant difference between the treatment groups was found for the analyses on the improvement from baseline. For the analysis on the improvement, there is no hint of added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven. For the analysis on worsening compared to the start of the study, a statistically significant difference was found to the disadvantage of luspatercept in comparison with the ACT. There is a hint of lesser benefit from luspatercept in comparison with the ACT.

Global health status, role functioning, emotional functioning, cognitive functioning and social functioning

For both the analyses on improvement and worsening, there was no statistically significant difference between the treatment groups for the outcomes of global health status, role functioning, emotional functioning, cognitive functioning and social functioning. In each case, there was no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs), severe adverse events (AEs) and discontinuation due to AEs

Until and including Week 24, there was no statistically significant difference between treatment groups for the outcomes of SAEs, severe AEs or discontinuation due to AEs. For each of them, there is no hint of greater or lesser harm from luspatercept in comparison with the ACT; greater or lesser harm is therefore not proven.

Nervous system disorders (severe AEs)

For the outcome of nervous system disorders (severe AEs), there is a statistically significant difference to the disadvantage of luspatercept versus the ACT. There is an indication of greater harm from luspatercept in comparison with the ACT.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug luspatercept in comparison with the ACT is assessed as follows:

In the overall consideration, there are both positive and negative effects of luspatercept compared to the ACT, with varying certainty of results and to varying degrees. These all are shown for outcomes with a shortened observation period.

For the outcome of transfusion avoidance, there is an indication of a non-quantifiable added benefit. On the negative side, the positive effect is offset by a hint of lesser benefit (extent: “considerable”) in the category of health-related quality of life and by an indication of greater harm (extent: “minor”) for serious/severe side effects.

The advantage of luspatercept administration, which was shown for the outcome of transfusion avoidance in the category "morbidity”, is therefore not reflected in other outcomes that could in principle be associated with transfusion avoidance: Alleviation of anaemia-related symptoms (e.g. fatigue and dyspnoea [on exertion] was not shown. In addition, there was no effect for individual dimensions of health-related quality of life (including global health status and social functioning) and there was even one negative effect (physical functioning). In summary, there is no hint of an added benefit of luspatercept over the ACT for patients with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS with ring sideroblasts, who had unsatisfactory response to or for whom erythropoetin-based therapy is ineligible.

Table 3 presents a summary of the probability and extent of added benefit of luspatercept.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Luspatercept – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS with ring sideroblasts, who had unsatisfactory response to or for whom erythropoetin-based therapy is ineligible[b]	Transfusion therapy with packed red blood cells (pRBC) as needed in combination with chelation therapy in accordance with the approval	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patients are in need of treatment and that an allogeneic stem cell transplantation is not an option for them at the time of treatment with luspatercept. If necessary, the use of epoetin, possibly in combination with G-CSF, may also be indicated in the present therapeutic indication.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; G-CSF: granulocyte colony-stimulating factor

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the context of market access in 2020. where, the G-BA had determined a non-quantifiable added benefit of luspatercept. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

I 2 Research question

The aim of the present report is to assess the added benefit of luspatercept versus the ACT in adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS with ring sideroblasts who had unsatisfactory response to or for whom erythropoetin-based therapy is ineligible.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of luspatercept

Therapeutic indication	**ACT[a]**
Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS with ring sideroblasts, who had unsatisfactory response to or for whom erythropoetin-based therapy is ineligible[b]	Transfusion therapy with packed red blood cells (pRBC) as needed in combination with chelation therapy in accordance with the approval
a. Presented is the ACT specified by the G-BA. b. It is assumed that the patients are in need of treatment and that an allogeneic stem cell transplantation is not an option for them at the time of treatment with luspatercept. If necessary, the use of epoetin, possibly in combination with G-CSF, may also be indicated in the present therapeutic indication. G-BA: Federal Joint Committee; G-CSF: granulocyte colony-stimulating factor; MDS: myelodysplastic syndrome	

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for deriving added benefit. This concurs with the company’s inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on luspatercept (status: 03 April 2023)
- bibliographical literature search on luspatercept (last search on 03 April 2023)
- search in trial registries/trial results databases for studies on luspatercept (last search on 4 April 2023)
- search on the G-BA website for luspatercept (last search on 4 April 2023)

To check the completeness of the study pool:

- search in trial registries for studies on luspatercept (last search on 24 May 2023); for search strategies, see Appendix I A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: luspatercept vs. placebo

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
ACE-536-MDS-001 (MEDALIST[c])	Yes	Yes	No	Yes [3,4]	Yes [5-7]	Yes [8,9]

a. Study for which the company was sponsor.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

RCT: randomized controlled trial

The study pool concurs with that of the company.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: luspatercept vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MEDALIST	RCT, double-blind, parallel-group	Adults with transfusion-dependent anaemia[b] due to MDS: ▪ with ring sideroblasts[c] ▪ with very low, low or intermediate risk[d] ▪ who had unsatisfactory response to or for whom erythropoetin-based therapy is ineligible[e] ▪ ECOG PS ≤ 2	Luspatercept[f] (N = 153) placebo[f] (N = 76)	Screening: ≤ 5 weeks treatment: ▪ primary treatment phase: 24 weeks[g] ▪ extension phase[h]: from Week 25 until the loss of the clinical benefit, disease progression, withdrawal of consent, unacceptable toxicity, death or switch to rollover study ACE-536-LTFU-001 observation[i]: ▪ outcome-specific, at most until death, withdrawal of consent, lost to follow-up, switch to rollover study ACE-536-LFTU-001 or end of study[j]	65 study centres in Belgium, Canada, France, Germany, Italy, Netherlands, Spain, Sweden, Turkey, United Kingdom, USA 02/2016–11/2020 data cut-offs: ▪ 08 May 2018 (primary analysis) ▪ 26 November 2020 (final analysis)	Primary: transfusion avoidance of ≥ 8 weeks during the primary treatment phase secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: luspatercept vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. The following criteria of transfusion dependence of packed red blood cells had to be met:

- Transfusion of an average of ≥ 2 packed red blood cell units/8 weeks for at least 16 weeks prior to randomization.
- No transfusion-free interval of ≥ 56 days within 16 weeks prior to randomization.
- Hb value of ≤ 10.0 g/dL at the time point of packed red blood cell transfusion or within 7 days before packed red blood cell transfusion.

c. According to the WHO classification of MDS [10], the proportion of ring sideroblasts in erythroid cells had to be ≥ 15% or ≥ 5% in the presence of an SF3B1 mutation.
d. According to the reviewed international prognostic score system (IPSS-R) for MDS [11].
e. Patients either had to have received prior treatment with ESA and had not shown adequate response, were not suitable for ESA (defined as unlikely response to ESA treatment with serum erythropoietin > 200 U/L) or had intolerance to this treatment.
f. Patients could receive packed red blood cell transfusions and/or iron chelation therapy if needed.
g. At the end of the primary treatment phase (at the visit in Week 25), the clinical benefit of the treatment with the study medication was assessed. The company named a reduction in the packed red blood cell transfusion burden and an increase in the Hb level compared to the baseline value as examples of proof of a clinical benefit. A conclusive list of criteria for the assessment of the clinical benefit is not available in the study documents.
h. From the visit in Week 25 onwards, double-blind treatment was only continued in both study arms if there was proven clinical benefit (e.g. reduction in packed red blood cell transfusion burden or increase in Hb level compared to baseline) and lack of disease progression according to International Working Group (IWG) criteria 2006 [12]. An assessment of clinical benefit/disease progression was performed at every 8th cycle of the extension phase on Day 1. The blinding was lifted after all patients had been treated with the study medication for 48 weeks or discontinued the study medication before week 48.
i. Outcome-specific information is provided in Table 8.
j. The study was terminated after all remaining patients had completed a follow-up phase of 3 years after the last dose of the study medication or had switched to the ACE-536-LFTU-001 rollover study before completion of the follow-up phase.

AE: adverse event; ECOG-PS: Eastern Cooperative Oncology Performance Status; ESA: erythropoiesis-stimulating agents; Hb: haemoglobin; IPSS-R: Revised International Prognostic Scoring System; IWG: International Working Group; MDS: myelodysplastic syndrome; N: number of randomized patients; RCT: randomized controlled trial; SF3B1: splicing factor 3B subunit 1; WHO: World Health Organization

Table 7: Characteristics of the interventions – RCT, direct comparison: luspatercept versus placebo (multipage table)

Study	Intervention	Comparison
MEDALIST	Luspatercept 1.0 mg/kg body weight, SC every 3 weeks (Day 1 of a 21-day cycle)	Placebo (volume equivalent to luspatercept) SC every 3 weeks (Day 1 of a 21-day cycle)
	Dose adjustments ▪ in patients who are not free of erythrocyte transfusions after at least 2 consecutive doses of the initial dose of 1.0 mg/kg, the dose should be increased by 1 dose level[a] each time to 1.33 mg/kg and 1.75 mg/kg (maximum 1.75 mg/kg once every 3 weeks, maximum total dose: 168 mg). ▪ dose delays or dose reductions - by 1 dose level each (minimum: 0.45 mg/kg once every 3 weeks) - were allowed in case of AEs or increased HB level.	
	Pretreatment ▪ ESA (recombinant human erythropoietin or darbepoetin alfa), G-CSF/GM-CSF[b] were allowed until 4 weeks before randomization ▪ packed red blood cell transfusions **disallowed pretreatment** ▪ disease-modifying substances for the treatment of MDS (e.g. immunomodulators [such as lenalidomide], HMA or IMiD)[c] ▪ luspatercept or sotatercept ▪ autologous or allogeneic stem cell transplantation ▪ the following substances/therapies within 5 weeks before randomization: ▫ cytotoxic chemotherapy ▫ corticosteroids[d] ▫ iron chelation therapy (except at a stable dose/with dose reduction since a time point of ≥ 8 weeks before randomization) ▫ other haematopoietic growth factors (e.g. interleukin 3) **allowed concomitant treatment** ▪ corticosteroids[d] ▪ iron chelation therapy - according to approval - at the investigator's discretion ▪ erythrocyte transfusions at the investigator's discretion in case of low Hb level[e], anaemia symptoms (e.g. haemodynamic or pulmonary impairment requiring treatment) or concomitant diseases (e.g. infection) ▪ supportive treatment with antibiotics, virostatics, antimycotics and/or supportive nutritional measures **nonpermitted concomitant treatment** ▪ cytotoxic, chemotherapeutic or targeted substances/therapies ▪ azacytidine, decitabine or other HMA ▪ lenalidomide, thalidomide or other IMiD ▪ ESA and other haematopoietic growth factors (e.g. interleukin 3) ▪ hydroxyurea ▪ arsenic trioxide ▪ interferon	

Table 7: Characteristics of the interventions – RCT, direct comparison: luspatercept versus placebo (multipage table)

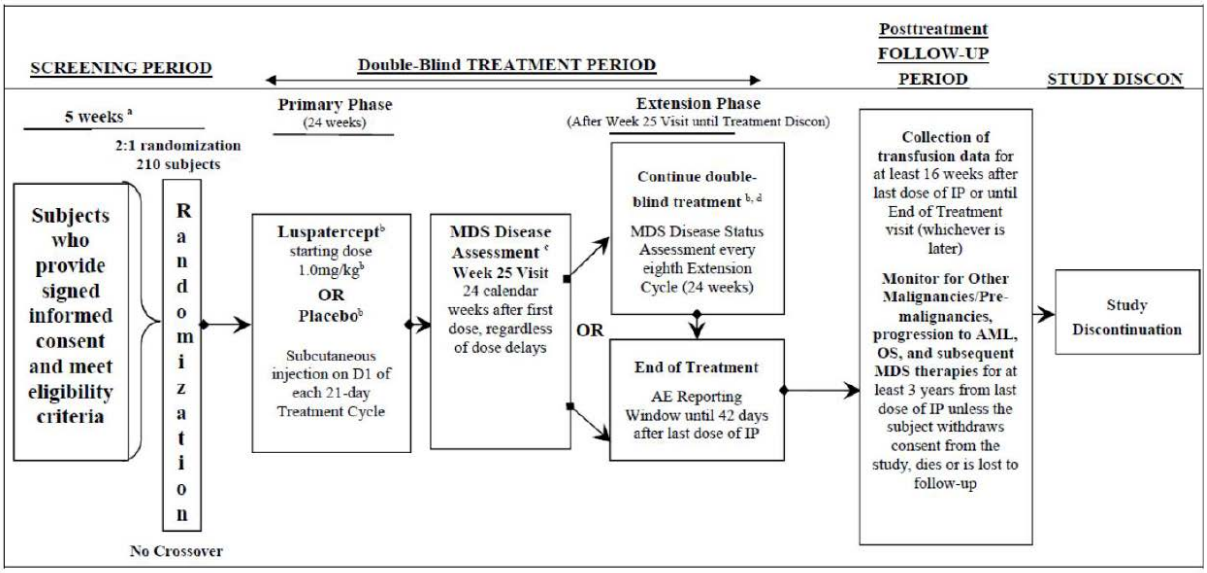
Study	Intervention	Comparison
a. The dose should not be increased more frequently than every 6 weeks (2 cycles). b. Administration of G-CSF/GM-CSF was permitted as concomitant treatment for febrile neutropenia or if clinically indicated in accordance with the approval. c. Patients could be included at the investigator's discretion if they had been treated with ≤ 2 doses of HMA ≥ 5 weeks prior to randomization or ≤ 1 week of lenalidomide. d. Administration of corticosteroids was permitted for the treatment of diseases other than MDS at a stable dose/with a dose reduction for ≥ 1 week prior to randomization. e. The administration of packed red blood cells should be delayed by ≥ 7 days and/or the transfusion burden should be reduced by ≥ 1 unit if the pre-transfusion Hb value increases by ≥ 1 g/dL compared to the Hb threshold value. The Hb threshold value is defined as mean of all documented Hb values of a patient prior to the transfusion of packed red blood cells in the 16-week interval before the first dose of the study medication (Day 1, Cycle 1). AE: adverse event; ESA: eerythropoiesis-stimulating agents; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; Hb: haemoglobin; HMA: hypomethylating agent; IMiD: immunomodulatory drug; MDS: myelodysplastic syndrome; RCT: randomized controlled trial; SC: subcutaneous		

The MEDALIST study was a double-blind, placebo-controlled RCT. The study enrolled adult patients with MDS with ring sideroblasts according to the World Health Organization (WHO) classification - proportion of erythroid cells of ≥ 15%, or ≥ 5% with simultaneous presence of an SF3B1 mutation [10] - and with very low, low or intermediate risk according to the revised International Prognostic Scoring System (IPSS-R) for MDS [11]. Moreover, patients had to have transfusion-dependent anaemia due to MDS. This was defined as an average requirement of ≥ 2 pRBC/8 weeks without a transfusion-free period of ≥ 56 days in the 16-week interval before the first dose of study medication. The Hb level was not allowed to be > 10.0 g/dL before the administration of pRBC. The patients had either received prior treatment with ESA (as mono/combination therapy) and had not shown adequate response, were not suitable for ESA - defined as unlikely response to ESA treatment with a serum erythropoietin level > 200 U/L - or had to be intolerant to ESA treatment.

Overall, 229 patients were included in the MEDALIST study and randomly allocated in a 2:1 ratio to treatment with luspatercept (N = 153) or placebo (N = 76). Randomization was stratified by the average transfusion burden at baseline (< 6 packed red blood cell units/8 weeks vs. ≥ 6 packed red blood cell units/8 weeks [in relation to 16 weeks before the first dose of study medication]) and the risk group according to IPSS-R at baseline (very low/low vs. intermediate).

After randomization, the MEDALIST study is divided into a treatment phase (comprising a primary treatment phase and an extension phase) and a (long-term) follow-up phase. The planned duration of the primary treatment phase was 24 weeks. From week 25, treatment

was continued in the extension phase only if there was a proven clinical benefit (e.g. reduction in packed red blood cell transfusion burden or increase in Hb level from baseline) and absence of disease progression (assessed at Week 25 and at every 8th cycle, Day 1 of the extension phase). Patients with treatment discontinuation in the primary treatment phase or in the extension phase were included in the (long-term) follow-up phase with the original randomized allocation was maintained. The long-term follow-up phase was planned for up to 3 years after the last dose of study medication. At no time during the study was a switch from placebo to luspatercept permitted.



a Historische Dokumentation der Transfusionsabhängigkeit sollte für mindestens 16 Wochen vor Randomisierung verfügbar sein (Anzahl transfundierte EK-Einheiten, Prätransfusions-Hb).
b Dosistitration bis maximal 1,75 mg/kg war erlaubt.
c Patient:innen, die nach Ermessen der Prüfärztin bzw. des Prüfarztes zu Woche 25 von der Behandlung profitiert haben, durften im Rahmen der doppelblinden Extensionsphase weiter behandelt werden bis die Kriterien zum Therapieabbruch erfüllt wurden.
d Eine Bewertung der Erkrankung entsprechend der Kriterien zur Woche 25-Visite musste zu Tag 1 von jedem 8. Behandlungszyklus durchgeführt werden.

[a] Historical documentation of transfusion dependency should be available for at least 16 weeks prior to randomization (number of transfused EC units, pre-transfusion Hb).
[b] Dose titration up to a maximum of 1.75 mg/kg was permitted.
[c] Patients who, at the investigator's discretion, benefited from treatment at Week 25 were allowed to continue treatment in the double-blind extension phase until the criteria for treatment discontinuation were met.
[d] An assessment of the disease according to the criteria for the visit at Week 25 had to be performed on Day 1 of every 8th treatment cycle.

Figure 1: Design of the MEDALIST study (figure of the company from Module 4 B of the dossier)

The study was unblinded after all patients had completed 48 weeks of treatment with the study medication or had discontinued treatment before Week 48. Subsequently, the

treatment of the remaining patients in the luspatercept arm could be continued as an open-label treatment.

Primary outcome of the MEDALIST study was transfusion avoidance of ≥ 8 weeks during the primary treatment phase. Additionally, patient-relevant outcomes were recorded on mortality, morbidity, health-related quality of life and side effects.

Uncertainties in the administration of luspatercept in the MEDALIST study

Treatment with luspatercept in the intervention arm was largely in compliance with the specifications of the SPC [13]. Deviating from this, a dose reduction below 0.8 mg/kg was permitted. As this only applied to 1 patient, this has no consequences for the assessment. According to the SPC, treatment with luspatercept should moreover be discontinued if patients do not notice a reduction in the transfusion burden after 9 weeks of treatment (3 doses) with the highest dose (1.75 mg/kg). Since the assessment of the clinical benefit in the MEDALIST study took place at the visit in Week 25, it is possible that patients in the luspatercept arm who were not free of packed blood cell transfusions during their treatment and should thus receive dose increases, received 2 luspatercept doses with the initial dose of 1.0 mg/kg (6 weeks), 2 consecutive doses of 1.33 mg/kg (6 weeks) and, in deviation, 4 instead of 3 consecutive doses of 1.75 mg/kg (12 weeks) up to and including Week 24 in accordance with the SPC. The company did not present any information on the proportion of patients treated with 4 consecutive doses (12 weeks) of the highest dose (1.75 mg/kg) up to the assessment of clinical benefit. Nevertheless, it is assumed that the possibility of a 12-week instead of a 9-week luspatercept administration at the highest dose until potential treatment discontinuation does not lead to relevant uncertainties in the interpretability of the study results.

Implementation of the ACT

For the present therapeutic indication, the G-BA specified transfusion therapy with packed red blood cells (pRBC) as needed in combination with chelation therapy in accordance with the approval as ACT.

Placebo was used in the comparator arm of the MEDALIST study. According to the study protocol, red blood cell transfusions were also permitted in both study arms at the investigator's discretion in the event of low Hb levels (compared to the individual Hb threshold value [average pre-transfusion Hb value in the 16-week interval before the first dose of study medication]), anaemia-related symptoms or concomitant diseases.

According to the guidelines, the indication for red blood cell transfusion is based on an assessment of the patient's overall clinical picture and should not be determined on the basis of laboratory parameters (e.g. Hb value) alone [14-16]. When deciding on the administration of pRBC, the anaemia-related symptoms and impairment of quality of life must be taken into account [14].

According to the study protocol, iron chelation therapy could be given at the investigator's discretion in accordance with the approval. According to the guidelines, chelation therapy is indicated for patients after transfusion of ≥ 20 packed red blood cell units or with a serum ferritin level of > 1000 µg/L to prevent a threatening iron overload of the organism [15,16]. 46% of the patients in the luspatercept arm and 53% in the placebo arm received pretreatment with iron chelators (see Table 9). Approx. 46% of patients in the luspatercept arm and 43% of the patients in the placebo arm received (at least) 1 iron chelator as concomitant treatment in the treatment phase (recorded until 42 days after the last dose of study medication).

Overall, it is assumed that in the comparator arm of the MEDALIST study, transfusion therapy with pRBC in combination with chelation therapy was carried out as needed in the sense of the ACT.

Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: luspatercept versus placebo

Study **outcome category** **outcome**	**Planned follow-up observation**
MEDALIST	
Mortality	
Overall survival	Until death, lost to follow-up, withdrawal of consent or until 3 years after the last dose of the study medication
Morbidity	
Transfusion avoidance	Until 16 weeks after the last dose of the study medication or until the EOT visit[a] (whichever occurred first)
Symptoms (EORTC QLQ-C30)	Until the EOT visit[a]
Health-related quality of life (EORTC QLQ-C30)	Until the EOT visit[a]
Side effects	
All outcomes in the side effects category	Until 42 days after the last dose of the study medication
a. The EOT visit should be carried out as soon as possible after the decision to discontinue treatment has been made. If treatment was discontinued at a regular study visit, all measurements scheduled at the end of treatment should have been completed at this time.	
EORTC: EOT: end of treatment; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial	

The observation periods for all outcomes in the categories "morbidity", "health-related quality of life" and "side effects" were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 42 days for side effects or 16 days for transfusion avoidance). To be able to draw a reliable conclusion over the total

study period, however, it would be necessary that also these outcomes - as was done for survival - are recorded over the total period.

Analysis time points provided by the company

At the final data cut-off (26 November 2020), the company specified up to 3 analysis dates for the completed MEDALIST study in Module 4 B, depending on the outcome category:

- 1st analysis date: up to and including Week 24 or up to Week 25
- 2nd analysis date: up to and including Week 48; analysis performed until all patients had reached Week 48 or had discontinued treatment before Week 48
- 3rd analysis date: until end of the study; analysis performed after all remaining patients had completed a follow-up phase of 3 years after the last dose of the study medication or had switched to the ACE-536-LFTU-001 rollover study before completion of the follow-up phase

For the present benefit assessment, analyses up to Week 24 or Week 25 were used for all outcomes in the category of morbidity, health-related quality of life and side effects. From Week 25 - after completion of the primary treatment phase - treatment with the study medication was continued during the extension phase in patients with a proven clinical benefit (e.g. reduction in packed red blood cell transfusion burden or increase in Hb level compared to baseline) and lack of disease progression. As the observation period in the MEDALIST study was linked to the end of treatment for all outcomes in the categories of morbidity, health-related quality of life and side effects (see Table 8), these outcomes were recorded from Week 25 onwards - with the exception of the planned follow-up after the end of treatment - only in patients in whom a clinical benefit could be determined at Week 25 and who had no progression of MDS. Since only 100 (65%) patients in the luspatercept arm and 26 (34%) patients in the placebo arm continued to be treated with the study medication after the visit at Week 25 (Day 1, Cycle 1 of the extension phase), this resulted in a clear difference in the treatment duration between the study arms and thus in clear differences in the estimated observation periods for outcomes relating to morbidity, health-related quality of life and side effects. In addition, no data are available on the administration of pRBC beyond 16 weeks after discontinuation of treatment with the study medication, as such administration was only recorded up to this point (see Table 8).

Deaths were recorded independently of the end of treatment. Therefore, overall survival on the basis of a time-to-event analysis at the final data cut-off (26 November 2020) was used as outcome of the category "mortality" for the present benefit assessment.

Characteristics of the study population

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: luspatercept versus placebo (multipage table)

Study characteristic category	Luspatercept N[a] = 153	Placebo N[a] = 76
MEDALIST		
Age [years], mean (SD)	71 (9)	71 (11)
Sex [f/m], %	39/61	34/66
Region, n (%)		
Europe	122 (80)	57 (75)
North America	31 (20)	19 (25)
Disease duration: time between first diagnosis and start of the study [months], median [Q1; Q3]	44.0 [23.2; 70.4]	36.1 [24.0; 68.6]
Risk group according to IPSS-R, n (%)		
Very low	18 (12)	6 (8)
Low	109 (71)	57 (75)
Intermediate	25 (16)	13 (17)
High	1 (< 1)	0 (0)
≥ 15% ring sideroblasts [% of erythroid cells], n (%)	153 (100)	76 (100)
SF3B1 mutation, n (%)		
Yes	141 (92)	65 (86)
No	12 (8)	10 (13)
Missing	0 (0)	1 (1)
Serum erythropoetin[b] [U/L], n (%)		
< 100	51 (33)	31 (41)
100 to < 200	37 (24)	19 (25)
200 to 500	43 (28)	15 (20)
> 500	21 (14)	11 (15)
Missing	1 (< 1)	0 (0)
Serum ferritin [µg/L], median [Q1; Q3]	1089.2 [679.0; 1662.0]	1122.1 [694.2; 1727.3]
Haemoglobin [g/dL] – mean (SD)	7.7 (0.8)	7.6 (0.8)
Transfusion burden, n (%)		
Packed red blood cell units/8 weeks[c]		
Mean (SD)	5.5 (2.8)	5.8 (3.0)
≥ 6 units	66 (43)	33 (43)
≥ 4 to < 6 units	41 (27)	23 (30)
< 4 units	46 (30)	20 (26)
Packed red blood cell units/24 weeks[d]		
Mean (SD)[e]	15.4 (7.7)	17.5 (8.9)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: luspatercept versus placebo (multipage table)

Study characteristic category	**Luspatercept N[a] = 153**	**Placebo N[a] = 76**
Pretreatment with ESA, n (%)	148 (97)	70 (92)
Reasons for discontinuation of ESA therapy, n (%)[f]		
Refractory	144 (97)	69 (99)
Intolerant	4 (3)	1 (1)
Pretreatment with iron chelators, n (%)	71 (46)	40 (53)
Pretreatment with G-CSF/GM-CSF, n (%)	51 (33)	22 (29)
Treatment discontinuation, n (%)[g]		
Until Week 24[h]	25 (16)[i]	8 (11)[i]
Until end of study[j]	153 (100)	76 (100)
Study discontinuation, n (%)		
Until week 24	ND	ND
Until end of study[k]	149 (97)	64 (84)

a. Number of randomized patients; values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. The baseline erythropoietin value is defined as highest erythropoietin value within 35 days before the first dose of study medication (Day 1, Cycle 1).
c. The baseline packed red blood cell transfusion burden is defined as the average of packed red blood cell units transfused per 8 weeks in relation to the 16-week interval prior to the first dose of the study medication (Day 1, Cycle 1).
d. The baseline packed red blood cell transfusion burden is defined as the number of packed red blood cell units transfused within 24 weeks, calculated on the basis of the packed red blood cell units transfused in the 16-week interval prior to the first dose of the study medication (Day 1, Cycle 1).
e. Data refer to patients who have completed 24 weeks of treatment in the intervention and control arm (see footnote "g").
f. Proportion referring to all patients with ESA pretreatment.
g. Number (%) of patients who completed 24 weeks of treatment in the intervention vs. the control arm: 128 (84) vs. 68 (90); number (%) of patients who completed 48 weeks of treatment in the intervention vs. the control arm: 83 (54) vs. 12 (16).
h. The company presented no reasons for the treatment discontinuation in the primary treatment phase in its dossier.
i. Institute's calculation.
j. This includes treatment discontinuations in the primary treatment phase and in the extension phase. Common reasons for treatment discontinuation in the intervention vs. the control arm were: no clinical benefit (48% vs. 66%), withdrawal of consent (12% vs. 13%), switch to the ACE-536-LTFU-001 rollover study (19% vs. 0%)
k. Common reasons for study discontinuation in the intervention arm versus the control arm were death (29% vs. 32%), switch to the ACE-536-LTFU-001 rollover study (34% vs. 28%), withdrawal of consent (23% vs. 17%).

ESA: eerythropoiesis-stimulating agents; F: female; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; IPSS-R: Revised International Prognostic Scoring System; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

Patient characteristics were largely balanced between the study arms. The mean age of the patients was 71 years; the majority of them were male (61% or 66%) and most were from Europe (80% or 75%). The majority (approx. 72%) of patients was in the low risk IPSS-R group and the average baseline value was 7.6 to 7.7 g/dL. The proportion of patients with an average packed red blood cell transfusion burden at baseline of ≥ 6 units/8 weeks is approx. 43%, followed by < 4 units/8 weeks and ≥ 4 to < 6 units/8 weeks (with less than 1 third each). 97% of the patients in the luspatercept arm and 92% of patients in the placebo arm received ESA pretreatment (as monotherapy or as combination therapy). In both study arms, a high proportion of patients were pretreated with a drug not approved for the therapeutic indication of MDS (darbepoetin alfa) (44% and 54% respectively). Almost all patients with (at least) 1 ESA pretreatment were refractory to ESA treatment at the start of the study.

At the final data cut-off (26 November 2020), all patients had discontinued treatment with the study medication. The most common reason for treatment discontinuation in both study arms was lack of clinical benefit.

Information on the course of the study

Table 10 shows the mean and median treatment duration of the patients and the mean and median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: luspatercept vs. placebo

Study **duration of the study phase** **outcome category**	**Luspatercept** **N = 153**	**Placebo** **N = 76**
MEDALIST		
Treatment discontinuation, n (%)	153 (100)	76 (100)
≥ 24 weeks completed	128 (83.7)	68 (89.5)
≥ 48 weeks completed	83 (54.2)	12 (15.8)
Treatment duration [weeks]		
Primary treatment phase[a]		
Median [Q1; Q3]	24.0 [ND; ND]	24.0 [ND; ND]
Mean (SD)	22.8 (3.9)	23.0 (3.3)
Entire treatment phase[b]		
Median [Q1; Q3]	50.9 [24.0; 137.9]	24.0 [24.0; 31.5]
Mean (SD)	76.7 (60.5)	31.7 (18.2)
Observation duration [months]		
Overall survival[c]		
Median [min; max]	34.1 [2.8; 47.7]	34.3 [1.7; 48.4]
Mean (SD)	29.7 (13.3)	29.3 (14.0)
Morbidity (transfusion avoidance, symptoms [EORTC QLQ-C30])	ND	ND
Health-related quality of life (EORTC QLQ-C30)	ND	ND
Side effects	ND	ND

a. Period from the 1st dose of the study medication (Day 1, Cycle 1) until and including Week 24.
b. Period from the 1st dose of the study medication (Day 1, Cycle 1) until the end of treatment (including extension phase).
c. Information on how the observation period was calculated is not available.

EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; ND: no data; Q1: first quartile; Q3: third quartile; QLQ-Q3: Quality of Life Questionnaire – Core 30; RCT: randomized controlled trial; SD: standard deviation

In the MEDALIST study, the median treatment duration was 50.9 weeks in the luspatercept arm and thus more than twice as long as in the placebo arm (24.0 weeks). This is due to the fact that treatment with the study medication was only continued after week 25 in patients with proven clinical benefit (e.g. reduction in packed red blood cell transfusion burden or increase in the Hb level compared to baseline) and no disease progression (see I 3.1 I 3.1); treatment was continued more frequently in the luspatercept arm than in the placebo arm. The respective proportion of patients who completed a 48-week study treatment was 54% in the luspatercept arm and 16% i the placebo arm. 84% of the patients in the luspatercept arm and 90% in the placebo arm completed a 24-week treatment with the study medication. The

median observation period for the outcome "overall survival" was about 34 months in both study arms. No information on the median or mean observation period was available for all outcomes of the categories "morbidity", “health-related quality of life” and "side effects". As the observation period for these outcomes was linked to the end of treatment (see Table 8), the observation periods differed significantly between the study arms and were shortened compared to the observation period for overall survival. For outcomes for which analyses up to Week 24 or Week 25 were used in the context of the present benefit assessment, a comparable observation duration between the study arms was shown at the selected analysis date.

Information on subsequent therapies

Table 11 shows the subsequent therapies patients received in the MEDALIST study after discontinuing the study medication.

Table 11: Information on subsequent therapies (≥ 2 patients in at least 1 study arm) – RCT, direct comparison: luspatercept vs. placebo

Study **drug class[a]** **drug[a]**	**Patients with subsequent therapy n (%)**	
	luspatercept **N = 153**	**placebo** **N = 76**
MEDALIST		
Total	64 (41.8)	43 (56.6)
Antineoplastic drugs	29 (45.3)	15 (34.9)
Azacitidine	14 (21.9)	6 (14.0)
Decitabine	6 (9.4)	3 (7.0)
Daratumumab	4 (6.3)	1 (2.3)
Busulfan	3 (4.7)	0 (0)
Hydroxycarbamide	3 (4.7)	1 (2.3)
Fludarabine	2 (3.1)	0 (0)
Imetelstat	1 (1.6)	2 (4.7)
All other therapeutic agents	23 (35.9)	19 (44.2)
Deferasirox	22 (34.4)	16 (37.2)
Deferipone	1 (1.6)	2 (4.7)
Deferoxamin mesilat	1 (1.6)	2 (4.7)
Antianaemics	17 (26.6)	13 (30.2)
Darbepoetin alfa	7 (10.9)	7 (16.3)
Epoetin alfa	5 (7.8)	4 (9.3)
Luspatercept	3 (4.7)	1 (2.3)
Erythropoietin	2 (3.1)	1 (2.3)
Immunosuppressants	16 (25.0)	11 (25.6)
Lenalidomide	15 (23.4)	11 (25.6)
Blood substitutes and perfusion solutions	6 (9.4)	3 (7.0)
Other blood products	6 (9.4)	3 (7.0)
Investigational preparation	6 (9.4)	1 (2.3)
Investigational preparation	6 (9.4)	1 (2.3)
Immunostimulants	2 (3.1)	8 (18.6)
Granulocyte colony-stimulating factor	1 (1.6)	3 (7.0)
Filgrastim	0 (0)	4 (9.3)
Anabolics for systemic use	0 (0)	2 (4.7)
Danazol	0 (0)	2 (4.7)

a. Assignment according to WHO Drug Dictionary, Version March 2017
b. Own calculation at drug class/drug level in relation to all patients with (at least 1) follow-up therapy after discontinuation of the study medication.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial; WHO: World Health Organization

After discontinuation of the study medication, there were no restrictions with regard to subsequent therapies - with the exception of a switch from placebo to luspatercept. In both study arms, some drugs were used as subsequent therapy that are not authorized for this therapeutic indication. The use of these drugs appears to be reasonable in principle due to the lack of treatment alternatives for patients with MDS.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: luspatercept vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
MEDALIST	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the MEDALIST study is rated as low.

Transferability of the study results to the German health care context

The company describes that overall, a good transferability of results of the MEDALIST study to the German healthcare context can be assumed, as the characteristics of the patients included in the study at its start would reflect the characteristics of patients with MDS living in Germany according to information in the MDS register in Düsseldorf (median age of onset 70 to 72 years and slightly higher incidence of the disease in men) [17-19]. In addition, the company states that due to the inclusion of patients with MDS in Europe and the USA - including 5 centres in Germany - the majority of patients were of white descent. Since most of the centres participating in the study are located in Western European or North American countries, it can be assumed that the standard of care is similar to that in Germany. From the company's perspective, there are no known systematic differences between the participating countries with regard to the treatment of patients with MDS.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - transfusion avoidance
  - symptoms recorded with the EORTC QLQ-C30
- Health-related quality of life
  - recorded with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 B).

Table 13 shows the outcomes for which data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: luspatercept versus placebo

Study	Outcomes							
	Overall survival	Transfusion avoidance[a]	Symptoms (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-C30)	SAEs[b]	Severe AEs[b, c]	Discontinuation due to AEs[b]	Nervous system disorders (SOC, severe AEs[c])
MEDALIST	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Defined as proportion of patients without packed red blood cell transfusion in the period before the first dose of study medication (Day 1, Cycle 1) up to and including Week 24.
b. Includes events of the underlying disease.
c. Severe AEs are operationalized as CTCAE grade ≥ 3. The severity of AEs for which no CTCAE criteria are defined was classified by the investigator using a 5-point scale (grade 1: mild; grade 2: moderate; grade 3: severe; grade 4: life-threatening; grade 5: fatal [see below]).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Notes on included outcomes

Transfusion avoidance

In Module 4 B of the dossier, the company presents analyses for the outcome of transfusion avoidance at different transfusion-free periods (≥ 8 weeks, ≥ 12 weeks, ≥ 16 weeks, ≥ 24 weeks, ≥ 36 weeks and ≥ 48 weeks) and analysis dates (up to and including Week 24, up to and including Week 48 and up to the end of the study). In its dossier, the company also presents data on the mean change in transfusion burden and the proportion of patients who fulfilled modified haematologic improvement–erythroid (HI-E) criteria based on the IWG criteria 2006. This latter outcome was described as a reduction in transfusion burden in the benefit assessment procedure D-561 for the drug luspatercept [20].

For patients in the present therapeutic indication, long-term or sustainable avoidance of transfusions while maintaining a defined minimum Hb level is a primary treatment goal, with the aim of controlling anaemia and anaemia-related symptoms while at the same time avoiding transfusions. The company justified the patient relevance of the outcome in Module 4 B of the dossier with the following 3 aspects:

- Avoiding transfusions is associated with the prevention of sometimes serious transfusion-related side effects (e.g. transfusion-related infections, allergic reactions) and a reduction in the stress and potential complications of transfusion-related iron absorption (prevention of secondary haemosiderosis).

- An increase and stabilisation of Hb levels alleviates the anaemia-related symptoms, which can improve the general condition of the often elderly, comorbid patients with MDS.
- The avoidance of transfusions and the improved control of anaemia are accompanied by psychosocial relief and a noticeable gain in time. Patients with MDS can once again organize their everyday lives with greater self-determination and flexibility.

It should be noted that the latter two aspects (anaemia-related symptoms [e.g. fatigue] and psychosocial aspects) can and should generally be mapped directly via patient-reported outcomes (PROs) in clinical trials. The company's argument that secondary complications (not usually recorded within the scope of the usual study duration) can be prevented by avoiding transfusions is comprehensible per se and avoiding transfusions is considered relevant to patients. In principle, however, it is necessary to collect data on the outcome of transfusion avoidance over the entire study period. However, due to the design of the MEDALIST study (treatment discontinuation in the absence of clinical benefit/disease progression at Week 25 with end of observation 16 weeks after the end of treatment), a valid interpretation and assessment of the results for this outcome at analysis dates after Week 24 is not possible (see Section I 3.1, analysis dates presented by the company).

A transfusion avoidance of 24 weeks (until the end of the primary treatment phase) is therefore used as the relevant period for the present assessment. Avoiding transfusions for 24 weeks is generally considered sufficient to be able to assume long-term avoidance of transfusions (freedom from transfusion). However, it remains uncertain whether the patients were actually free of red blood cell transfusions beyond the primary treatment phase in all cases and whether secondary complications (organ complications due to secondary haemosiderosis) could actually be avoided to a relevant extent in the patient population concerned here. Due to these described uncertainties, the observed effects in this outcome can therefore not be quantified (see Section I 5.2).

Transfusion avoidance must be distinguished from a reduction in the transfusion burden, as a mere reduction in the transfusion volume is not per se relevant to the patient. Consequently, the results on the outcome "reduction in transfusion burden" are not used for the present benefit assessment and are only presented as supplementary information in I Appendix D.

Symptoms and health-related quality of life (EORTC QLQ-C30)

In the MEDALIST study, the EORTC QLQ-C30 was used to assess symptoms and health-related quality of life. The EORTC QLQ-C30 is a generic instrument that has been validated for the recording of symptoms and health-related quality of life in patients with cancer and can be supplemented by numerous additional modules. In addition, the EORTC QLQ-C30 is the most frequently used instrument in studies in the therapeutic indication of MDS [21]. Since the main

symptoms of MDS (e.g. fatigue and [exertional] dyspnoea) are queried via the EORTC QLQ-C30, this instrument is used for the benefit assessment in the present situation.

In Module 4 B of the dossier, the company presents responder analyses for the symptom and functional scales of the EORTC QLQ-C30 for the proportion of patients with an improvement or deterioration by ≥ 10 points and ≥ 15 points compared to baseline (respective scale range 0 to 100). For the benefit assessment procedure, only analyses for the response criterion of 10 points are to be presented in the dossier for EORTC questionnaires [22]. These are used for the benefit assessment.

According to the guidelines, the treatment goal of patients with low-risk MDS is a reduction in the cytopenia-associated symptoms and an improvement of the quality of life [15,16,23]. In the MEDALIST study, however, a similarly high proportion of patients showed an improvement or deterioration by the response criterion of 10 points over the course of the study. Therefore, both operationalizations are taken into account in the present data situation and the results for the assessment of added benefit are interpreted using the overall picture.

Side effects

In the MEDALIST study, the severity of AEs was classified according to CTCAE, Version 4.03. AEs whose severity is not defined according to CTCAE were assessed by the investigator using a 5-point scale as follows:

- Grade 1 - mild: temporary or mild discomfort; no restriction of activity; no medical intervention/therapy required
- Grade 2 - moderate: mild to moderate limitation of activity, some support may be required; no or minimal medical intervention/therapy required
- Grade 3 - severe: significant limitation of activity, usually some support is required; medical intervention/therapy required, hospitalization is possible
- Grade 4 - life-threatening: extreme limitation of activity, major support required; major medical intervention/therapy required, hospitalization or hospice care likely
- Grade 5 - fatal: the event is fatal

Due to a sufficient similarity between the 5 criteria selected by the company and the 5 generic CTCAE criteria [24], this approach has no consequences for the benefit assessment.

With the dossier, the company does not present any additional analyses for the overall rate of SAEs, severe AEs and discontinuations due to AEs in which events of the underlying disease, e.g. anaemia (PT), MDS (PT) or transformation to acute myeloid leukaemia (PT), are not taken into account. The company justified its approach by stating that no events were identified in the MEDALIST study for which an alternative aetiology (e.g. a worsening pre-existing condition

or the study therapy) could be excluded with sufficient certainty. The overall rates of SAEs, severe AEs and discontinuations due to AEs including disease-related events are used for the present benefit assessment, as only a few such events occurred and in the present data situation it is assumed that these events included in the respective analysis have no relevant impact on the study results.

Notes on the QoL-E instrument

In Module 4 B of the dossier, the company presents supplementary analyses on the outcome of health-related quality of life, recorded with the QoL-E [25]. This is a specific questionnaire for recording PROs in patients with MDS. Version 3.0 of the QoL-E was used in the MEDALIST study. As this version of the questionnaire is not validated and there are also uncertainties in the score formation, these analyses are not used for the present benefit assessment. The company justified the supplementary presentation with the G-BA's benefit assessment of luspatercept, in which the QoL-E, version 3.0, was already not considered at an earlier point in time due to insufficient validity [20].

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: luspatercept versus placebo

Study	Study level	Outcomes							
		Overall survival	Transfusion avoidance[a]	Symptoms (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-C30)	SAEs[b]	Severe AEs[b, c]	Discontinuation due to AEs[b]	Nervous system disorders (SOC, severe AEs[c])
MEDALIST	L	L	L	H[d]	H[d]	L	L	L	L

a. Defined as proportion of patients without packed red blood cell transfusion in the period before the first dose of study medication (Day 1, Cycle 1) up to and including Week 24.
b. Includes events of the underlying disease.
c. Severe AEs are operationalized as CTCAE grade ≥ 3. The severity of AEs for which no CTCAE criteria are defined was classified by the investigator using a 5-point scale (grade 1: mild; grade 2: moderate; grade 3: severe; grade 4: life-threatening; grade 5: fatal [for reasons, see I 4.1, side effects]).
d. Large proportion of patients (> 20%) not considered in the analysis.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

The risk of bias of the results was rated as low for all outcomes, except the outcomes of symptoms and health-related quality of life. The risk of bias of the results on the symptoms outcomes (recorded with the EORTC QLQ-C30) and health-related quality of life (recorded with the EORTC QLQ-C30) was rated as high due to the high proportion of patients (> 20%) who were not included in the analyses.

I 4.3 Results

Table 15 and Table 16 summarize the results of the comparison of luspatercept versus placebo in adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS with ring sideroblasts who had unsatisfactory response to or for whom erythropoetin-based therapy is unsuitable. Where necessary, calculations conducted by the Institute are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves on the time-to-event analysis for the outcome of overall survival are presented in I Appendix B of the full dossier assessment, and the results on common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment. Results on the outcomes of reduction in transfusion burden and overall hospitalization are presented in I Appendix D of the full dossier assessment.

Table 15: Results (mortality) – RCT, direct comparison: luspatercept vs. placebo

Study **outcome category** **outcome**	**Luspatercept**		**Placebo**		**Luspatercept vs. placebo**
	N	**median time to event in months [95% CI]** **patients with event n (%)**	**N**	**median time to event in months [95% CI]** **patients with event n (%)**	**HR [95% CI]; p-value[a]**
MEDALIST					
Mortality					
Overall survival[b]	153	46.0 [42.0; NC] 45 (29.4)	76	NR [43.1; NC] 24 (31.6)	0.99 [0.59; 1.64]; 0.958

a. HR and CI: Cox regression model, p-value: log-rank test, each stratified according to IPSS-R risk group at baseline (very low or low versus intermediate) and average transfusion burden at baseline (≥ 6 packed red blood cell units/8 weeks vs. < 6 packed red blood cell units/8 weeks).

b. Analysis refers to the period from the 1st dose of the study medication (Day 1, Cycle 1) until the final data cut-off (26 November 2020).

CI: confidence interval; HR: hazard ratio; IPSS-R: Revised International Prognostic Scoring System; n: number of patients with event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial

Table 16: Results (morbidity, health-related quality of life, side effects) – RCT, direct comparison: luspatercept versus placebo (multipage table)

Study outcome category outcome	Luspatercept		Placebo		Luspatercept vs. placebo
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
MEDALIST					
Morbidity					
Transfusion avoidance[b]	153	20 (13.1)	76	1 (1.3)	9.84 [1.36; 71.31]; 0.024
Symptoms (EORTC QLQ-C30)					
Improvement by ≥ 10 points[c]					
Fatigue	109	32 (29.4)	54	24 (44.4)	0.67 [0.44; 1.01]; 0.056
Nausea and vomiting	110	17 (15.5)	54	5 (9.3)	1.71 [0.67; 4.38]; 0.263
Pain	109	25 (22.9)	54	14 (25.9)	0.86 [0.49; 1.50]; 0.591
Dyspnoea	106	24 (22.6)	54	16 (29.6)	0.77 [0.45; 1.31]; 0.335
Insomnia	108	27 (25.0)	54	18 (33.3)	0.77 [0.47; 1.25]; 0.290
Appetite loss	109	22 (20.2)	53	9 (17.0)	1.21 [0.59; 2.46]; 0.602
Constipation	110	31 (28.2)	53	13 (24.5)	1.16 [0.67; 2.01]; 0.601
Diarrhoea	110	11 (10.0)	53	6 (11.3)	0.84 [0.33; 2.15]; 0.718
Deterioration by ≥ 10 points[d]					
Fatigue	109	50 (45.9)	54	14 (25.9)	1.76 [1.07; 2.89]; 0.026
Nausea and vomiting	110	17 (15.5)	54	7 (13.0)	1.19 [0.51; 2.74]; 0.690
Pain	109	27 (24.8)	54	14 (25.9)	0.99 [0.56; 1.73]; 0.962
Dyspnoea	106	30 (28.3)	54	10 (18.5)	1.56 [0.81; 3.01]; 0.186
Insomnia	108	19 (17.6)	54	18 (33.3)	0.53 [0.30; 0.93]; 0.028
Appetite loss	109	22 (20.2)	53	10 (18.9)	1.06 [0.53; 2.14]; 0.860
Constipation	110	15 (13.6)	53	5 (9.4)	1.42 [0.54; 3.76]; 0.477
Diarrhoea	110	16 (14.5)	53	5 (9.4)	1.59 [0.57; 4.40]; 0.376
Health-related quality of life					
EORTC QLQ-C30					
Improvement by ≥ 10 points[e]					
Global health status	110	31 (28.2)	53	12 (22.6)	1.24 [0.69; 2.25]; 0.476
Physical functioning	110	25 (22.7)	54	18 (33.3)	0.70 [0.42; 1.16]; 0.163
Role functioning	110	30 (27.3)	54	18 (33.3)	0.82 [0.50; 1.34]; 0.425
Emotional functioning	110	18 (16.4)	53	11 (20.8)	0.81 [0.41; 1.59]; 0.542
Cognitive functioning	110	29 (26.4)	53	14 (26.4)	1.01 [0.58; 1.76]; 0.968
Social functioning	110	26 (23.6)	53	16 (30.2)	0.76 [0.45; 1.30]; 0.322

Table 16: Results (morbidity, health-related quality of life, side effects) – RCT, direct comparison: luspatercept versus placebo (multipage table)

Study outcome category outcome	Luspatercept		Placebo		Luspatercept vs. placebo
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
Deterioration ≥ 10 points[f]					
Global health status	110	33 (30.0)	53	11 (20.8)	1.47 [0.80; 2.67]; 0.213
Physical functioning	110	34 (30.9)	54	7 (13.0)	2.33 [1.12; 4.87]; 0.024
Role functioning	110	35 (31.8)	54	19 (35.2)	0.90 [0.58; 1.41]; 0.652
Emotional functioning	110	28 (25.5)	53	14 (26.4)	0.99 [0.57; 1.72]; 0.973
Cognitive functioning	110	29 (26.4)	53	17 (32.1)	0.83 [0.50; 1.36]; 0.458
Social functioning	110	36 (32.7)	53	16 (30.2)	1.10 [0.68; 1.79]; 0.687
Side effects[b]					
AEs[g] (supplementary information)	153	145 (94.8)	76	70 (92.1)	–
SAEs[g]	153	40 (26.1)	76	16 (21.1)	1.25 [0.75; 2.08]; 0.395
Severe AEs[g, h]	153	55 (35.9)	76	27 (35.5)	1.01 [0.70; 1.45]; 0.978
Discontinuation due to AEs[g]	153	12 (7.8)	76	4 (5.3)	1.54 [0.50; 4.79]; 0.454
Nervous system disorders (SOC, severe Aesh,[h, i])	153	8 (5.2)	76	0 (0)	8.50 [0.50; 145.34]; 0.044[j, k]

a. RR, CI and p-value using the CMH method, stratified by IPSS-R risk group at baseline (very low or low versus intermediate) and average transfusion burden at baseline (≥ 6 packed red blood cell units/8 weeks vs. < 6 packed red blood cell units/8 weeks).
b. Analysis refers to the period from the 1st dose of the study medication (Day 1, Cycle 1) until Week 24.
c. Proportion of patients with a score decrease by ≥ 10 points from baseline by Week 25, at a scale range of 0 to 100. Lower (decreasing) values indicate an improvement of symptoms.
d. Proportion of patients with score increase by ≥ 10 points from baseline at Week 25, at a scale range of 0 to 100. Higher (increasing) values indicate a deterioration of symptoms.
e. Proportion of patients with score increase by ≥ 10 points from baseline at Week 25, at a scale range of 0 to 100. Higher (increasing) values indicate an improvement in health-related quality of life.
f. Proportion of patients with a score decrease by ≥ 10 points from baseline by Week 25, at a scale range of 0 to 100. Lower (decreasing) values indicate a deterioration of health-related quality of life.
g. Includes events of the underlying illness.
h. Operationalized as CTCAE grade ≥ 3. The severity of AEs for which no CTCAE criteria were defined was classified by the investigator using a 5-point scale (grade 1: mild; grade 2: moderate; grade 3: severe; grade 4: life-threatening; grade 5: fatal [for reasons, see Section I 4.1, side effects]).
i. Mainly includes the following events (MedDRA coding): syncope (PT) and presyncope (PT).
j. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test; CSZ method according to [26]); in case of 0 events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms.
k. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

AE: adverse event; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; IPSS-R: Revised International Prognostic Scoring System; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire–Core 30; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

Based on the available information, at most indications, e.g. of an added benefit, can be determined for the outcomes of overall survival, transfusion avoidance and for all outcomes of the side effects category, while at most hints, e.g. of an added benefit, can be derived for the outcomes on symptoms and health-related quality of life due to the associated high risk of bias [for reasons, see Section I 4.2].

Mortality

Overall survival

For the outcome of overall survival, there was no statistically significant difference between the treatment groups up to the final data cut-off (16 November 2020). There was no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Transfusion avoidance

Up to and including Week 24, a statistically significant difference was found in favour of luspatercept in comparison with the ACT for the outcome of transfusion avoidance. There is an indication of added benefit of luspatercept in comparison with watchful waiting.

Symptoms (EORTC QLQ-C30)

For the outcomes on symptoms, recorded with the EORTC QLQ-C30, responder analyses were used on both improvement and worsening by ≥ 10 points at Week 25 (see Section I 4.1).

Fatigue and insomnia

For the outcomes of fatigue and insomnia, there was no statistically significant difference between treatment groups for the analyses on the improvement from baseline. For the analysis of worsening compared to the start of the study, a statistically significant difference to the disadvantage of luspatercept compared to the ACT was shown for the outcome “fatigue”, whereas a statistically significant difference in favour of luspatercept over the ACT was shown for the outcome “insomnia”. However, for these two outcomes, this difference is no more than marginal. In each case, there was no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Nausea and vomiting, pain, dyspnoea, appetite loss, constipation and diarrhoea

For the analyses on both improvement and worsening, no statistically significant difference between the treatment groups was shown for each of the following outcomes: “nausea and vomiting”, “pain”, “dyspnoea”, “appetite loss”, “constipation” and “diarrhoea”. In each case, there was no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

For the outcomes on health-related quality of life, recorded with the EORTC QLQ-C30, responder analyses were used on both improvement and worsening by ≥ 10 points at Week 25 (see Section I 4.1).

Physical functioning

For the outcome of physical functioning, no statistically significant difference between the treatment groups was found for the analyses on the improvement from baseline. For the analysis on the improvement, there is no hint of added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven. For the analysis on worsening compared to the start of the study, a statistically significant difference was found to the disadvantage of luspatercept in comparison with the ACT. There is a hint of lesser benefit from luspatercept in comparison with the ACT.

Global health status, role functioning, emotional functioning, cognitive functioning and social functioning

For both the analyses on improvement and worsening, there was no statistically significant difference between the treatment groups for the outcomes of global health status, role functioning, emotional functioning, cognitive functioning and social functioning. In each case, there was no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs and discontinuation due to AEs

Until and including Week 24, there was no statistically significant difference between treatment groups for the outcomes of SAEs, severe AEs or discontinuation due to AEs. For each of them, there is no hint of greater or lesser harm from luspatercept in comparison with the ACT; greater or lesser harm is therefore not proven.

Nervous system disorders (severe AEs)

For the outcome of nervous system disorders (severe AEs), there is a statistically significant difference to the disadvantage of luspatercept versus the ACT. There is an indication of greater harm from luspatercept in comparison with the ACT.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for the present benefit assessment:

- sex (female versus male)
- age (≤ 64 years versus 65 to 74 years versus ≥ 75 years)
- average transfusion burden at baseline (< 4 packed red blood cell units/8 weeks vs. ≥ 4 to 6 packed red blood cell units/8 weeks vs. ≥ 6 packed red blood cell units/8 weeks)

Interaction tests are conducted when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup results in the dossier do not reveal any effect modifications. No subgroup analyses were pre-specified for the outcome "overall survival" and these are not available in the company's dossier.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of each added benefit at outcome level is assessed based on the results presented in Section I 4 (see Table 17).

Determination of the outcome category for symptom outcomes

For the morbidity outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Transfusion avoidance

Information on the assignment to the severity category is insufficient for the outcome "transfusion avoidance". The outcome of transfusion avoidance was therefore assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Symptoms

Fatigue and insomnia (EORTC QLQ-C30)

The median baseline value in the fatigue symptom scale was 33.3 points in the luspatercept arm and 38.9 points in the placebo arm, and the median baseline value in the insomnia symptom scale (scale range in each case from 0 to 100 points, lower values mean better symptoms) was 33.3 points. At the start of the study, this thus corresponds to mild to moderate symptoms. Since even most of the patients with worsening symptoms (with an increase in the score of ≥ 10 points compared to baseline) do not have severe symptoms at Week 25, the outcomes of fatigue and insomnia (EORTC QLQ-C30 symptom scale) are each assigned to the outcome category of non-severe/non-severe symptoms/late complications.

Table 17: Extent of added benefit at outcome level: luspatercept versus ACT (multipage table)

Outcome category **outcome**	**Luspatercept vs. placebo** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Outcomes observed over the entire study duration		
Mortality		
Overall survival	46.0 vs. NA HR: 0.99 [0.59; 1.64] p = 0.958	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Transfusion avoidance	13.1% vs. 1.3% RR: 9.84 [1.36; 71.31] RR: 0.10 [0.01; 0.74][c] p = 0.024 probability: indication	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "non-quantifiable"[d]
Symptoms (EORTC QLQ-C30)		
Improvement by ≥ 10 points		
Fatigue	29.4% vs. 44.4% RR: 0.67 [0.44; 1.01] p = 0.056	Lesser/added benefit not proven
Nausea and vomiting	15.5% vs. 9.3% RR: 1.71 [0.67; 4.38] p = 0.263	Lesser/added benefit not proven
Pain	22.9% vs. 25.9% RR: 0.86 [0.49; 1.50] p = 0.591	Lesser/added benefit not proven
Dyspnoea	22.6% vs. 29.6% RR: 0.77 [0.45; 1.31] p = 0.335	Lesser/added benefit not proven
Insomnia	25.0% vs. 33.3% RR: 0.77 [0.47; 1.25] p = 0.290	Lesser/added benefit not proven
Appetite loss	20.2% vs. 17.0% RR: 1.21 [0.59; 2.46] p = 0.602	Lesser/added benefit not proven
Constipation	28.2% vs. 24.5% RR: 1.16 [0.67; 2.01] p = 0.601	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: luspatercept versus ACT (multipage table)

Outcome category **outcome**	**Luspatercept vs. placebo** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Diarrhoea	10.0% vs. 11.3% RR: 0.84 [0.33; 2.15] p = 0.718	Lesser/added benefit not proven
Deterioration by ≥ 10 points		
Fatigue	45.9% vs. 25.9% RR: 1.76 [1.07; 2.89] RR: 0.57 [0.35; 0.93][c]; p = 0.026	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[e]
Nausea and vomiting	15.5% vs. 13.0% RR: 1.19 [0.51; 2.74] p = 0.690	Lesser/added benefit not proven
Pain	24.8% vs. 25.9% RR: 0.99 [0.56; 1.73] p = 0.962	Lesser/added benefit not proven
Dyspnoea	28.3% vs. 18.5% RR: 1.56 [0.81; 3.01] p = 0.186	Lesser/added benefit not proven
Insomnia	17.6% vs. 33.3% RR: 0.53 [0.30; 0.93] p = 0.028	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[e]
Appetite loss	20.2% vs. 18.9% RR: 1.06 [0.53; 2.14] p = 0.860	Lesser/added benefit not proven
Constipation	13.6% vs. 9.4% RR: 1.42 [0.54; 3.76] p = 0.477	Lesser/added benefit not proven
Diarrhoea	14.5% vs. 9.4% RR: 1.59 [0.57; 4.40] p = 0.376	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30		
Improvement by ≥ 10 points		
Global health status	28.2% vs. 22.6% RR: 1.24 [0.69; 2.25] p = 0.476	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: luspatercept versus ACT (multipage table)

Outcome category **outcome**	**Luspatercept vs. placebo** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Physical functioning	22.7% vs. 33.3% RR: 0.70 [0.42; 1.16] p = 0.163	Lesser/added benefit not proven
Role functioning	27.3% vs. 33.3% RR: 0.82 [0.50; 1.34] p = 0.425	Lesser/added benefit not proven
Emotional functioning	16.4% vs. 20.8% RR: 0.81 [0.41; 1.59] p = 0.542	Lesser/added benefit not proven
Cognitive functioning	26.4% vs. 26.4% RR: 1.01 [0.58; 1.76] p = 0.968	Lesser/added benefit not proven
Social functioning	23.6% vs. 30.2% RR: 0.76 [0.45; 1.30] p = 0.322	Lesser/added benefit not proven
Deterioration by ≥ 10 points		
Global health status	30.0% vs. 20.8% RR: 1.47 [0.80; 2.67] p = 0.213	Lesser/added benefit not proven
Physical functioning	30.9% vs. 13.0% RR: 2.33 [1.12; 4.87] RR: 0.43 [0.21; 0.89][c] p = 0.024 probability: “hint”	Outcome category: health-related quality of life $CI_u < 0.90$ lesser benefit, extent: considerable
Role functioning	31.8% vs. 35.2% RR: 0.90 [0.58; 1.41] p = 0.652	Lesser/added benefit not proven
Emotional functioning	25.5% vs. 26.4% RR: 0.99 [0.57; 1.72] p = 0.973	Lesser/added benefit not proven
Cognitive functioning	26.4% vs. 32.1% RR: 0.83 [0.50; 1.36] p = 0.458	Lesser/added benefit not proven
Social functioning	32.7% vs. 30.2% RR: 1.10 [0.68; 1.79] p = 0.687	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: luspatercept versus ACT (multipage table)

Outcome category **outcome**	**Luspatercept vs. placebo** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	26.1% vs. 21.1% RR: 1.25 [0.75; 2.08] p = 0.395	Greater/lesser harm not proven
Severe AEs	35.9% vs. 35.5% RR: 1.01 [0.70; 1.45] p = 0.978	Greater/lesser harm not proven
Discontinuation due to AEs	7.8% vs. 5.3% RR: 1.54 [0.50; 4.79] p = 0.454	Greater/lesser harm not proven
Nervous system disorders (severe AEs)	5.2% vs. 0.0% RR: 8.50 [0.50; 145.34] p = 0.044 probability: indication	Outcome category: serious/severe side effects greater harm, extent: "minor"[f]

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. See Section I 4.1, Transfusion avoidance, for reasons.
e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
f. Discrepancy between p-value (exact) and CI (asymptomatic) due to different calculation methods; the extend is rated as "minor".

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire – Core 30; RR: relative risk; SAE: serious adverse event

I 5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of luspatercept in comparison with the ACT

Positive effects	Negative effects
Outcomes observed over the entire study duration	
–	–
Outcomes with shortened observation period	
Non-serious/non-severe symptoms/late complications ▪ transfusion avoidance: indication of an added benefit – extent: "non-quantifiable"	–
–	Health-related quality of life ▪ EORTC QLQ-C30 – physical functioning (deterioration by ≥ 10 points): hint of lesser benefit – extent "considerable"
–	Serious/severe side effects ▪ nervous system disorders (severe AEs): indication of greater harm – extent: minor
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire – Core 30	

In the overall consideration, there are both positive and negative effects of luspatercept compared to the ACT, with varying certainty of results and to varying degrees. These all are shown for outcomes with a shortened observation period.

For the outcome of transfusion avoidance, there is an indication of a non-quantifiable added benefit. On the negative side, the positive effect is offset by a hint of lesser benefit (extent: “considerable”) in the category of health-related quality of life and by an indication of greater harm (extent: “minor”) for serious/severe side effects.

The advantage of luspatercept administration, which was shown for the outcome of transfusion avoidance in the category "morbidity”, is therefore not reflected in other outcomes that could in principle be associated with transfusion avoidance: Alleviation of anaemia-related symptoms (e.g. fatigue and dyspnoea [on exertion] was not shown. Moreover, there was no effect for individual dimensions of health-related quality of life (including global health status and social functioning) and there was even one negative effect (physical functioning). In summary, there is no hint of an added benefit of luspatercept over the ACT for patients with transfusion-dependent anaemia due to very low, low and

intermediate-risk MDS with ring sideroblasts, who had unsatisfactory response to or for whom erythropoetin-based therapy is ineligible.

Table 19 summarizes the result of the assessment of the added benefit of luspatercept in comparison with the ACT.

Table 19: Luspatercept – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS with ring sideroblasts, who had unsatisfactory response to or for whom erythropoetin-based therapy is ineligible[b].	Transfusion therapy with packed red blood cells (pRBC) as needed in combination with chelation therapy in accordance with the approval	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patients are in need of treatment and that an allogeneic stem cell transplantation is not an option for them at the time of treatment with luspatercept. If necessary, the use of epoetin, possibly in combination with G-CSF, may also be indicated in the present therapeutic indication.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; G-CSF: granulocyte colony-stimulating factor

The assessment described above deviates from that by the company, which derived an indication of considerable added benefit.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the context of market access in 2020. where, the G-BA had determined a non-quantifiable added benefit of luspatercept. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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